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Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: Results from a longitudinal study

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Summary The aim of the present study was to evaluate the presence of psychiatric diseases/symptoms in transsexual patients and to compare psychiatric distress related to the hormonal intervention in a one year follow-up assessment. We investigated 118 patients before starting the hormonal therapy and after about 12 months. We used the SCID-I to determine major mental disorders and functional impairment. We used the Zung Self-Rating Anxiety Scale (SAS) and the Zung Self-Rating Depression Scale (SDS) for evaluating self-reported anxiety and depression. We used the Symptom Checklist 90-R (SCL-90-R) for assessing self-reported global psychological symptoms. Seventeen patients (14%) had a DSM-IV-TR axis I psychiatric comorbidity. At enrollment the mean SAS score was above the normal range. The mean SDS and SCL-90-R scores were on the normal range except for SCL-90-R anxiety subscale. When treated, patients reported lower SAS, SDS and SCL-90-R scores, with statistically significant differences. Psychiatric distress and functional impairment were present in a significantly higher percentage of patients before starting the hormonal treatment than after 12 months (50% vs. 17% for anxiety; 42% vs. 23% for depression; 24% vs. 11% for psychological symptoms; 23% vs. 10% for functional impairment). The results revealed that the majority of transsexual patients have no psychiatric comorbidity, suggesting that transsexualism is not necessarily associated with severe comorbid psychiatric findings. The condition, however, seemed to be associated with subthreshold anxiety/depression, psychological symptoms and functional impairment. Moreover, treated patients reported less psychiatric distress. Therefore, hormonal treatment seemed to have a positive effect on transsexual patients' mental health.

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1. Introduction

The Gender Identity Disorder (GID) is characterized by a strong and persistent identification with the opposite sex and persistent discomfort with one's own biological sex or the roles assigned to it (APA, 2000). Gender Identity Disorder or transsexualism may also be suspected in children, therefore in adolescents and young adults this condition may be a continuation of a previous condition or develop de novo.

When clinicians attempt to assess treatment protocols for the care of transsexual patients, two difficulties become apparent: the absence of criteria for defining the subjects as eligible for a specific treatment and the lack of consensus on the therapeutic approach, which could differ by country. However, most of the countries involved in transsexual patients' care have accepted the standards of care developed by the World Professional Association for Transgender Health (WPATH) (Coleman et al., 2012) which are based on a somatic and psychiatric assessment before the initiation of a hormono-surgical treatment. The psychiatric evaluation consists of verifying the following main criteria: to accurately diagnose the Gender Identity Disorder (Diagnostic and Statistical Manual criteria fulfilled); to verify the persistence of the request; and to diagnose/treat any comorbid psychiatric conditions.

Previous reports on the psychiatric comorbidity among transsexual patients revealed contradictory findings. Some researches reported that transsexual patients show a high prevalence of psychiatric comorbidity (A Campo et al., 2003; Hepp et al., 2005; Heylens et al., 2013). Instead, other studies showed a low level of psychopathology (Gómez-Gil et al., 2009; Hoshiai et al., 2010), also in Italian samples (Fisher et al., 2013). However, psychiatric comorbidities and functional impairment seemed to be associated with a lack of hormone treatment (Gómez-Gil et al., 2009).

For most patients transsexualism may be a stressful condition and may cause clinical distress or impairment in important areas of functioning (Gómez-Gil et al., 2009; Colizzi et al., 2013). Cross-sex hormonal therapy interests transsexual patients as a means of matching their gender identification and physical appearance. It induces the development of the secondary sex characteristics of the desired sex and diminishes those of the biological sex (Hembree et al., 2009) and seems to be linked to better mental health and quality of life (Newfield et al., 2006; Gómez-Gil et al., 2012).

Although the impact of sex reassignment surgery on satisfaction or quality of life has been previously described (Weyers et al., 2009), very few data are available concerning the impact of hormonal therapy on the well-being of subjects. A recent meta analysis of the impact of hormonal therapy and sex reassignment on quality of life and psychosocial outcomes identified only five studies that specifically examined hormonal therapy (Murad et al., 2011). Research assessments have examined the impact of hormonal therapy on the outcomes of transformation satisfaction (Kuiper and Cohen-Kettenis, 1988), psychological profile (Leavitt et al., 1980), cognitive function (Slabbekoorn et al., 1999; Miles et al., 2006), and emotional repercussions (Slabbekoorn et al., 1999). Moreover, only one study has recently examined the disparity between the untreated and the hormone treated transsexual patients in terms of mental health, showing in a cross-sectional study that hormone treated transsexual patients report less social distress, anxiety and depression, independently of any type of surgical intervention (Gómez-Gil et al., 2012). In addition, a research showed that hormonal treatment has improved transsexual patients' general health, while there was no significant difference in the quality of life between transsexual patients who had undergone genital or breast surgery and transsexual patients who did not have these surgeries, suggesting the importance of hormonal treatment (Motmans et al., 2012). However, the lack of significant differences between pre-genital and post-genital surgery groups could be partly explained by the circumstance that the pre-genital surgery group could be fairly sure that they were on track for genital surgery in the future (Motmans et al., 2012). There have been several studies into the possible positive effects of surgical therapy in transsexualism (Weyers et al., 2009); in contrast, literature on the effect of cross-sex hormone therapy especially on mental health is very limited.

To our knowledge, transsexual patients' psychiatric comorbidity (qualitative data) and self-reported psychiatric distress (quantitative data) in the same sample have not been previously evaluated. In the same way, differences in psychiatric distress related to the hormonal treatment in a longitudinal study have not been previously reported. In fact, due to their cross-sectional design, previous studies did not demonstrate a direct positive effect of hormonal treatment in transsexual patients' quality of life (Gorin-Lazard et al., 2012) and mental health (Gómez-Gil et al., 2012). Longitudinal studies, instead, conduct observations of the same subjects over a period of time and can establish sequences of events and detect changes in the characteristics of the target population.

This study had two main aims: the first was to evaluate the presence of psychiatric diagnoses/distress in transsexual patients attending a gender identity unit, through diagnostic clinical interviews (psychiatric comorbidity and functional impairment evaluation) and self reported scales (anxiety, depression and psychological symptoms measurement). The second aim was to compare psychiatric distress with regard to the hormonal intervention in a longitudinal study. On the basis of our own clinical experience, we hypothesized that the majority of transsexual patients have no psychiatric comorbidity. Moreover, we suggested a high rate of psychiatric distress in untreated transsexual patients and a significant reduction of perceived anxiety, depression, psychological symptoms and functional impairment in transsexual patients after the beginning of hormonal treatment.

2. Materials and methods

2.1. Study design and sample

This study incorporated a longitudinal design and was conducted in the Gender Identity Unit of the Bari University Psychiatric Department. A consecutive series of 118 patients was evaluated for transsexualism from 2008 to 2012.

The inclusion criteria for the longitudinal study were as follows: 18 years or older, diagnosis of Gender Identity Disorder in adults according to the Diagnostic and Statistical Manual, fourth edition text revision (DSM-IV TR) criteria (APA,

Table 1 Prevalence of psychiatric comorbidity measured with SCID-I in transsexual patients.

	Transsexual patients evaluated for the study $n = 118$ n (%)	Transsexual patients included in the longitudinal study $n = 107$ n (%)	Transsexual patients excluded from the longitudinal study $n = 11$ n (%)
Without PC	101 (85.6%)	101 (94.4%)	
With PC	17 (14.4%)	6 (5.6%)	11 (100%)
T II BD	2 (1.7%)	1 (0.9%)	1 (9.1%)
MDD	3 (2.5%)	1 (0.9%)	2 (18.2%)
DD	3 (2.5%)	1 (0.9%)	2 (18.2%)
GAD	6 (5.1%)	2 (2%)	4 (36.3%)
SA	2 (1.7%)	1 (0.9%)	1 (9.1%)
DID	1 (0.9%)	—	1 (9.1%)

SCID-I, Structured Clinical Interview for DSM-IV-TR Axis-I Disorders; PC, Psychiatric Comorbidity; T II BP, Type II Bipolar Disorder; MDD, Major Depressive Disorder; DD, Dystymic Disorder, GAD, Generalized Anxiety Disorder; SA, Substance Abuse; DID, Dissociative Identity Disorder.

2000), inclusion in a standardized cross sex hormonal reassignment procedure following the agreement of a multidisciplinary team, the absence of an unstable psychiatric comorbidity as assessed by the Structured Clinical Interview for DSM-IV-TR Axis-I Disorders SCID-I, and being a native Italian speaker. The presence of any neurologic, metabolic or intersexual pathology has been considered an exclusion principle. These assessments were performed by psychiatrists, psychologists, endocrinologists and gynecologists specializing in transsexualism management, using unstructured and structured interviews containing psychometric scales, and hematologic and chromosome profile evaluations. All these assessment were performed during a period of about 24 weeks (enrollment period). The study was proposed to each consecutive eligible subject by the care team during a routine visit.

During the enrollment period 17 transsexual patients (14%; 11 Male to Female, MtF; 6 Female to Male, FtM) received a diagnosis based on the DSM-IV-TR criteria (Table 1). Because of their unstable psychiatric comorbidity, 11 patients (7 MtF and 4 FtM) were treated and excluded from the longitudinal study (included only in the transsexual patients' psychiatric comorbidity evaluation). The other 6 patients (4 MtF and 2FtM) had a stable treated psychiatric comorbidity and were included in the longitudinal study (Table 1). The eligible 107 individuals approached for participation in this study agreed to participate in the study. Participation was voluntary, and the responses to the self-reported questionnaires were anonymous and confidential. All participants provided written informed consent.

Hormonal treatment for MtF transsexual patients consisted of transdermal estradiol gel (1.82 ± 0.53 mg/day), in association with oral cyproterone acetate (100 mg/day). The androgen administration schedule in FtM patients consisted of testosterone administered as intramuscular injections of a testosterone esters depot (250 mg every 26.24 ± 2.71 days). All the patients in this study received hormonal therapy after the enrollment period of multidisciplinary evaluation to obtain a ruling on eligibility for a cross-sex hormonal reassignment procedure. Only 9 transsexual patients (8%) [7 MtF (9%) and 2 FtM (7%)] passed in their desired gender role without hormonal treatment; all the other transsexual patients required hormonal treatment before undertaking gender role reassignment. During the study period all the individuals underwent a ''real-life experience''. This experience involves living full time and continually in the desired gender role, including dressing and interacting socially at home and work as the desired gender. The unit has adopted the standards of care guidelines of the World Professional Association for Transgender Health (WPATH) (Coleman et al., 2012). No patient had undergone any type of surgical intervention.

2.2. Data collection

The following data were collected:

1. Sociodemographic information: age, gender identity (Male to Female, MtF, Female to Male, FtM), education level (years of study), partnership status (not single/single), living arrangement (partner or parents/alone), employment status (no/yes) and sexual orientation (same biological sex or not).
2. Psychiatric history: psychiatric treatment/diagnose (no/yes) and functional impairment (evaluated with SCID-I).

The following three self-reported questionnaires were performed after the enrollment period, when the transsexual patients received the eligibility for the cross-sex hormonal treatment (phase 1), and after about 12 months (53.23 weeks $\pm$ 19.42 days) of hormone therapy (phase 2) to assess self-reported anxiety, depression and psychological symptoms.

1. Anxiety: symptoms of current anxiety were assessed using Zung Self-Rating Anxiety Scale (SAS), a quantitative 20-item self-report questionnaire (Zung, 1971). The symptoms included in the instrument are those most commonly found in general anxiety disorder (Zung, 1971, 1980). The ratings cover the week prior to the evaluation. Each item is rated for severity, in terms of the intensity, duration and frequency of each symptom. A four-point scale is used ranging from 1 (None or insignificant) to 4 (Severe). Raw scores are added (range, 20—80) and the total is transformed by dividing by 80 and multiplying by 100, giving an Index score in a range from 25 (low anxiety) to 100 (high anxiety) (Zung, 1974). Zung proposed a cutting-point of 44/45 to indicate clinically significant anxiety (Zung, 1980). Scores of 45—59 indicate minimal to moderate anxiety; 60—74 suggests marked to severe

anxiety; 75 or higher indicates extreme anxiety (Zung and Cavenar, 1980). The reliability of the SAS reported a split-half coefficient of 0.71 and alpha was 0.85 (Zung, 1980). Alpha was 0.69 for unaffected subjects, and 0.81 for psychiatric patients (Jegede, 1977). Zung has validated the scale showing that each item is capable of distinguishing significantly between patients with anxiety and unaffected adults (Zung, 1980). Zung summarized mean scores from various countries, showing broadly comparable results (Zung, 1980).

2. Depression: symptoms of current depression were assessed using Zung Self-Rating Depression Scale (SDS), a 20-item self-report questionnaire developed to quantify the severity of current depression in patients with depressive disorder (Zung, 1967). It has subsequently been used in clinical studies to monitor changes following treatment (Schotte et al., 1996). For each item, respondents indicate the severity (frequency, duration and intensity) with which they experience the symptom or feeling, either at the time of testing (Zung, 1967) or in the previous week (Zung, 1986). A four-point scale is used ranging from 1 (None or insignificant) to 4 (Severe). Item scores are added to form a total ranging from 20 to 80, with higher scores indicating increasing depression. The raw score is then converted to an Index by dividing by 80 and multiplying by 100, producing a range from 25 to 100 (Schotte et al., 1996). Most guidelines for interpreting results suggest that Index scores of less than 50 are within the normal range, scores of 50—59 indicate minimal or mild depression, 60 to 69 moderate-to-marked depression, and scores above 70 severe depression (Zung, 1967). Several studies have estimated the internal consistency of the SDS in sample sizes ranged from 100 to 225. Alphas ranging from 0.75 to 0.95 have been reported (Jegede, 1976; Toner et al., 1988). Split-half reliability was estimated at 0.73 (Zung, 1986) and at 0.81 (Yesavage et al., 1983). Review articles and a meta-analysis have found an overall impression of moderate validity in identifying treatment effects, levels of depression, and significant differences among patients with depression, anxiety, other psychiatric patients and controls (Hedlund and Vieweg, 1979; Lambert et al., 1986).

3. Psychological symptoms: symptoms were evaluated by the Symptom Checklist 90-Revised (SCL-90-R), a questionnaire ideally suited to quickly assess a patient's type and severity of self-reported symptoms and provide a measure of current psychological status over a 1-week interval (Derogatis, 1994). The SCL-90-R consists of a series of 90 descriptions of symptoms that a patient rates in term of their severity on a five-point scale (ranging from 0 = Not at all to 4 = Extremely). The symptoms are scored around nine different dimensions: somatization (SOM), obsessive—compulsive (O-C), interpersonal sensitivity (I-S) (feelings of personal inadequacy and inferiority), depression (DEP), anxiety (ANX), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PAR), and psychoticism (PSY). A global index of distress is also measured, the Global Severity Index (GSI). The wide diversity validity of over 1000 studies suggest that the SCL-90-R can be used with a wide variety of respondents (diagnostic groups and non-patients). The reliability of the SCL-90-R has consistently been good. The internal consistencies (coefficient alpha) concerning the nine primary symptom scales based on psychiatric outpatients ranged from a low of 0.79 for paranoid ideation to a high of 0.90 for depression (Derogatis and Savitz, 1999). Internal consistency for ''symptomatic volunteers'' was slightly lower and ranged from a low of 0.77 for psychoticism to a high of 0.90 for depression (Derogatis and Savitz, 1999). Test—retest reliability over a 1-week interval ranged from a low of 0.78 for hostility to a high of 0.90 for phobic anxiety. Most coefficients were in the mid-80s (Derogatis, 1994). Test—retest reliability over a 2-week interval was a quite high 0.91 for the GSI, indicating that this is a stable measure over time (Derogatis, 1994). The professional literature supports the use of the SCL-90-R as a valid and reliable measure of psychological symptoms that can be used for screening and the assessment of treatment outcomes (Derogatis, 1994; Derogatis and Savitz, 1999). SCL-90-R has been recently validated in its Italian version (Prunas et al., 2012). Cutting score of this scale of psychiatric screening is widely recommended that GSI = 1.00 points. An increase of the scores over than 1.00 indicates increase in the individual's suffering of psychological symptoms and the best index of the scale. Scores of underline 1.00 indicates healthy subjects (Derogatis, 1994).

2.3. Statistical analysis

All analyses were conducted using STATA 10 (Stata Corp, USA). The difference of the proportion of MtF and FtM transsexual patients among partnership status, living arrangement, employment status and sexual orientation were evaluated using the Chi-square (or Fisher's Exact test for 2×2 tables). The difference of the percentage of transsexual patients with symptoms of anxiety, depression, psychological symptoms and functional impairment according to the hormonal treatment were evaluated using the McNemar's test. The comparison of age and level of education between MtF and FtM were performed using independent t-tests. The comparison of SAS, SDS and SCL-90-R between untreated (phase 1) and treated transsexual patients (phase 2) were performed using dependent t-tests. The significance level was set at $p < 0.05$.

2.4. Ethics

All the patients gave their informed consent to participate in the study, which had been approved by the Ethical Committee of the Medical Faculty, University of Bari (983/CE), in agreement with the Declaration of Helsinki.

3. Results

3.1. Sample description

3.1.1. Sociodemographic information

Sociodemographic information of the 107 transsexual patients included in this study (age, level of education, partnership status, living arrangement, employment status and sexual orientation) were reported in Table 2. MtF and FtM did not show differences between their sociodemographic characteristics.

3.1.2. Psychiatric history

Of the 107 transsexual patients included in the longitudinal study, the 6 patients with a stable psychiatric comorbidity (5.6%) were taking psychiatric drugs at the time of study for

Table 2 Transsexual patients' sociodemographic characteristics.

	Transsexual patients $n = 107$ M (SD)	MtF $n = 78$ (73%) M (SD)	FtM $n = 29$ (27%) M (SD)
Age	29.20 (7.56)	29.25 (7.27)	29.09 (8.48)
Level of education (years of study)	11.04 (3.52)	10.89 (3.66)	11.46 (3.09)
	n (%)	n (%)	n (%)
Partnership status			
Single	34 (32)	24 (31)	10 (34)
Not single	73 (68)	54 (69)	19 (66)
Living arrangement			
With parents/partner	85 (79)	63 (81)	22 (76)
Alone	22 (21)	15 (19)	7 (24)
Employment status			
Employed	71 (66)	51 (65)	20 (69)
Not employed	36 (34)	27 (35)	9 (31)
Sexual orientation			
Homosexual	101 (94)	75 (96)	26 (90)
Heterosexual	6 (6)	3 (4)	3 (10)

MtF, Male to Female; FtM, Female to Male.

2.78 years ± 1.69 months. Molecules, dosages and administration modalities were stable for 1.93 years ± 0.90 months. The remaining 101 (94.4%) patients did not receive a standard diagnosis based on the DSM-IV-TR criteria due to absence or an insufficient number/duration of symptoms (Table 1). No patient has developed a psychiatric comorbidity during the study. There were no significant differences in sociodemographic variables between transsexual patients with unstable psychiatric comorbidity ($n = 11$) excluded from the study, transsexual patients without psychiatric comorbidity ($n = 101$) enrolled in the study, and transsexual patients with stable psychiatric comorbidity ($n = 6$) enrolled in the study.

3.2. Anxiety, depression and psychological symptoms scores in transsexual patients before (phase 1) and after (phase 2) cross-sex hormonal treatment

In phase 1 the mean SAS score ($M = 44.91$; SD = 9.59) was slightly above the normal range (25—44) (Table 3). Instead, the mean SDS (Table 4) and SCL-90-R (Table 5) scores were on the normal range except for SCL-90-R anxiety subscale ($M = 1.05$; SD = 3.86) (Table 5). Dependent sample t-test tested the relation between SAS, SDS and SCL-90-R scores and the hormonal treatment. When treated with cross-sex hormonal treatment (phase 2) transsexual patients reported lower SAS, SDS and SCL-90-R scores than at enrollment (phase 1), with statistically significant differences (Tables 3—5).

3.3. Percentages of transsexual patients with symptoms of anxiety, depression, psychological symptoms and functional impairment according to the hormonal treatment

Overall, 53 transsexual patients (50%) at enrollment (phase 1) and 18 transsexual patients (17%) under hormonal treatment (phase 2) experienced symptoms of anxiety (score > 44) (Table 3). The same pattern was found for symptoms of depression (score > 49); the percentages were significantly higher in phase 1 (45 patients, 42%) than in phase 2 (24 patients, 23%) (Table 4). In the same way, in phase 1, 26 transsexual patients (24%) experienced

Table 3 Means, standard deviations and prevalence of symptoms of anxiety measured with SAS scale in transsexual patients before (phase 1) and after cross-sex hormonal treatment (phase 2), and statistical comparisons with t-test and Chi-square.

SAS	Transsexual patients before HT (phase 1) ($n = 107$)	Transsexual patients after HT (phase 2) ($n = 107$)		Statistical comparisons	
(Normal range)	M (SD)	M (SD)		t	p
(25—44)	44.91 (9.59)	37.90 (8.97)		5.71	<.001
Anxiety (scores)	n (%)	n (%)	χ^2		p
None (25—44)	54 (50%)	89 (83%)	33.03[a]		<.001
Mild (45—59)	46 (43%)	15 (14%)			
Moderate (60—74)	5 (5%)	3 (3%)			
Severe (75—100)	2 (2%)	—			

SAS, Zung Self-Rating Anxiety Scale; HT, cross-sex hormonal treatment.
[a] Comparison between transsexual patients without symptoms of anxiety and transsexual patients with some symptoms of anxiety.

Table 4 Means, standard deviations and prevalence of symptoms of depression measured with SDS scale in transsexual patients before (phase 1) and after cross-sex hormonal treatment (phase 2), and statistical comparisons with *t*-test and Chi-square.

SDS	Transsexual patients before HT (phase 1) (n = 107)	Transsexual patients after HT (phase 2) (n = 107)		Statistical comparisons	
(Normal range)	*M* (SD)	*M* (SD)		*t*	*p*
(25—49)	48.04 (10.5)	39.98 (10.79)		6.16	<.001
Depression (scores)	*n* (%)	*n* (%)	χ^2		*p*
None (25—49)	62 (58%)	83 (77%)	19.05[a]		<.001
Mild (50—59)	31 (29%)	18 (17%)			
Moderate (60—69)	10 (9%)	6 (6%)			
Severe (70—100)	4 (4%)	—			

SDS, Zung Self-Rating Depression Scale; HT, cross-sex hormonal treatment.
[a] Comparison between transsexual patients without symptoms of depression and transsexual patients with some symptoms of depression.

significant psychological symptoms (SCL-90-R GSI score > 1); in phase 2, instead, only 4 transsexual patients (4%) referred significant psychological symptoms (Table 5). Finally, of 107 patients enrolled in the study 25 transsexual patients in phase 1 (23%) and 11 transsexual patients in phase 2 (10%) expressed substantial functional impairment (Table 5).

3.4. Differences on mental health due to the biological sex and the gender role reassignment according to the hormonal treatment

There were no significant differences between MtF and FtM transsexual patients' mental health (anxiety, depression and psychological symptoms scores; prevalence of anxiety, depression, psychological symptoms and functional impairment), both in phase 1 and phase 2. In the same way there were no significant differences on mental health between patients who passed in their desired gender role without hormonal treatment and all the other transsexual patients who required hormonal treatment before undertaking gender role reassignment, both in phase 1 and phase 2.

4. Discussion

In the past few decades, the literature has addressed transsexual patients' quality of life, satisfaction and various other outcomes such as sexual functioning after sex reassignment surgery (Bonierbale et al., 2004; Klein and Gorzalka, 2009; Weyers et al., 2009). Few data are available regarding the role of hormonal therapy in the well-being of transsexual patients without sex reassignment surgery. However, these data should provide relevant information for

Table 5 Means, standard deviations and prevalence of symptoms of psychological symptoms measured with SCL-90-R scale and of functional impairment measured with SCID-I in transsexual patients before (phase 1) and after cross-sex hormonal treatment (phase 2), and statistical comparisons with *t*-test and Chi-square.

	Transsexual patients before HT (phase 1) (n = 107)	Transsexual patients after HT (phase 2) (n = 107)		Statistical comparisons	
(Normal values <1)	*M* (SD)	*M* (SD)		*t*	*p*
SOM (SCL-90-R)	0.54 (0.59)	0.36 (0.33)		2.71	.008
O-C (SCL-90-R)	0.75 (0.66)	0.50 (0.40)		3.43	<.001
I-S (SCL-90-R)	0.97 (0.82)	0.65 (0.48)		3.78	<.001
DEP (SCL-90-R)	0.83 (0.74)	0.51 (0.49)		3.82	<.001
ANX (SCL-90-R)	1.05 (0.94)	0.54 (0.56)		5.25	<.001
HOS (SCL-90-R)	0.57 (0.69)	0.38 (0.37)		2.76	.007
PHOB (SCL-90-R)	0.53 (0.61)	0.35 (0.33)		2.79	.006
PAR (SCL-90-R)	0.92 (0.75)	0.65 (0.47)		3.08	.003
PSY (SCL-90-R)	0.61 (0.59)	0.46 (0.38)		2.30	.023
GSI (SCL-90-R)	0.74 (0.63)	0.48 (0.31)		4.09	<.001
	n (%)	*n* (%)	χ^2		*p*
GSI > 1 (SCL-90-R)	26 (24%)	12 (11%)	12.07[a]		<.001
FI (SCID-I)	25 (23%)	11 (10%)	12.07		<.001

SCL-90-R, Symptom Checklist 90-Revised; SCID-I, Structured Clinical Interview for DSM-IV-TR Axis-I Disorders; SOM, somatization; O-C, obsessive—compulsive; I-S, interpersonal sensitivity, DEP, depression; ANX, anxiety; HOS, hostility; PHOB, phobic anxiety; PAR, paranoid ideation; PSY, psychoticism; GSI, Global Severity Index; FI, Functional Impairment; HT, cross-sex hormonal treatment.
[a] Comparison between transsexual patients with a significant GSI (>1) and transsexual patients without a significant GSI (<1).

both transsexual patients and their healthcare providers. In light of the importance of this information, several interesting results of the current study must be discussed.

The most important result from this prospective study was that cross-sex hormonal treatment is associated with better mental health in transsexualism. In fact, when treated with cross-sex hormonal treatment transsexual patients reported less anxiety, depression, psychological symptoms and functional impairment. Another important finding is that, although untreated patients did not report depression and anxiety mean scores suggestive of severe mental diseases, the absence of hormonal treatment was associated with transient situational disturbances scores (mean score of 48 for depression, mean score of 45.8 for anxiety) (Zung, 1974, 1980). Moreover, this study contributed to the current discussions about categorical/hetero evaluation and dimensional/self evaluation systems. Of the 118 consecutive patients evaluated for this study, 17 transsexual patients (14%) had a DSM-IV-TR axis I psychiatric comorbidity. Of 107 patients enrolled in the longitudinal study, instead, about 50% of patients reported some symptoms of depression or anxiety and nearly one out of four patients experienced significant psychological symptoms and functional impairment.

The differences of the percentages of transsexual patients with psychiatric disorders/distress according to the categorical/hetero evaluation or the dimensional/self evaluation diagnostic approach seems to be attributable to the number, duration and severity of symptoms. On one hand, the categorical-based diagnostic approach showed several patients with substantial functional impairment that did not receive a standard diagnosis based on the DSM-IV-TR criteria due to an insufficient number/duration of symptoms [of 25 (23%) untreated patients with functional impairment only 6 (5.6%) with a DSM-IV-TR axis I comorbidity]. On the other hand, the dimensional-based diagnostic approach showed 50% of patients with some symptoms of anxiety and/or depression but only 7 patients (7%) with moderate to severe anxiety and 14 patients (13%) with moderate to severe depression.

Individuals requiring psychiatric intervention may not receive a standard diagnosis based on the DSM-IV-TR due to an insufficient number or duration of symptoms (Johnson et al., 1992). Functional impairment is part of the definition of mental disorders, as a benchmark to differentiate mental disorder from ''normal problem of living'' (APA, 2000). As such, functional impairment may contribute to the identification of clinically relevant symptoms, as a description or count of symptoms alone cannot capture the impact of disease at an individual and societal level, much of which is person and context dependent (Prince et al., 2011). Patients with substantial functional impairment who do not meet diagnostic criteria are regarded as having subthreshold disorders (Judd et al., 1994), unique conditions demanding recognition (Helmchen and Linden, 2000). Many studies have shown the clinical relevance of subthreshold depression and anxiety as risk factors for future full-syndromal depressive and anxiety disorders (Karsten et al., 2011).

Results of this longitudinal study underline the suffering of non-treated transsexual patients and the probable favorable evolution of their mental health with hormonal therapy in a sex reassignment procedure. According to our results, the association between hormonal treatment and lower anxiety, depression, psychological symptoms and functional impairment seems to be an indirect effect of hormone therapy. Estrogens and androgens, in fact, may plausibly exert different and prevalently negative effects on mood and mental distress. Estrogens may make individuals more prone to anxiety and depression (Asscheman et al., 1989). Androgens would promote feelings of euphoria and energy (Su et al., 1993) or stress and hostility (King et al., 2005). Hence, one would expect that transsexual patients might display an increase in mental distress due to hormonal treatment and that treated MtF patients might show a higher prevalence of anxiety and depression than treated FtM patients. Nevertheless, our study found a positive effect of hormonal treatment on depression and anxiety, both in MtF and FtM transsexual patients. Moreover, we did not find differences between MtF and FtM transsexual patients when gender was included in the statistical analyses. Therefore, as previously reported by Kuiper and Cohen-Kettenis, our results could not support the hypothesis of a direct relation between the hormone therapy itself and the patients' subjective well-being (1988). For most transsexual patients, a strong and persistent identification with the opposite sex and discomfort with one's own sex is a life challenge that often creates distress (Colizzi et al., 2013) and carries potential stigmatization (Matsumoto et al., 2009; Hoshiai et al., 2010). Transsexual patients face major stress in managing their gender identity and psychiatric/psychological symptoms may be considered as a reaction to the non-satisfaction connected to their incongruent image. Hormone therapy induces desired changes in transsexual patients' body features and shape and this could translate into a better quality of life for the patient himself. Thanks to the body changes obtained, transsexual patients could experience a reduction of self-reported distress (Gómez-Gil et al., 2012; Colizzi et al., 2013). In particular, the change in gender role among all the hormone treated transsexual patients included in this study should probably directly influence the self-reported better mental health. However, the few transsexual patients who passed in their desired gender role without hormonal treatment did not show a lower prevalence of mental distress than patients who required hormonal treatment before undertaking gender role reassignment, both in phase 1 and phase 2. Therefore, the sex reassignment procedure may reinforce the gender affirmation with a better social recognition. Moreover, the initiation of the hormonal treatment could have a psychological meaning which per se could be fundamental in reducing distress. As reported in previous studies, in fact, our clinical experience suggests that transsexual patients attending a gender unit are pleased in the knowledge that the hormonal therapy will be performed within a reasonable time and refer a distress reduction because of their accepted and understood requirements (Kuiper and Cohen-Kettenis, 1988). In any case, data are too limited to express conclusively.

Mental health promotion as a concept involves making efforts to improve the well-being of individuals and communities, and is different from prevention of mental disorders, which, in essence, may be a part and parcel of mental health promotion efforts (World Health Organization, 2004). Any action that is taken for protecting and improving mental health can be a part of mental health promotion

(Christodoulou and Kontaxakis, 1994; World Health Organization, 1995). Therefore, hormonal treatment in transsexualism could be considered a therapeutic action that increases the patients' well-being and mental health.

Although dosage, molecule nature, length of treatment, and administration modalities of hormone therapy were sufficiently standardized in this study, future studies should integrate these parameters to more precisely examine the role of hormones in the life of transsexual patients. Understanding these mechanisms is extremely important if one wants to grant early enough interventions to transsexual patients who seem to live a very distressful condition. This article has showed the potential for early hormonal treatment intervention to reduce anxiety, depression, psychological symptoms and functional impairment in transsexualism. These results could help us develop health policies that treat the transsexual patients' health as ''a state of complete physical, mental and social well-being and not merely an absence of disease or infirmity'', in accordance with the WHO health definition (Naidoo and Wills, 2000).

A limit of our study was that we did not evaluate important variables that could modulate the hormonal treatment response such as patients' life experiences, presence of supportive/unsupportive parents or partners, societal oppression, stigmatization/discrimination, coping styles and other psychological mechanisms. Moreover, the generalization of our results may be limited by the fact that patients were recruited from a specialized gender unit in Italy where the care pathway provides continuous psychological support to the patients' emotional and behavioral changes that occur during the cross-sex hormonal treatment. We cannot exclude a positive effect of psychological treatment on mental health improvement. Therefore, psychological intervention could partially explain our findings. We suspect that findings could be likely different in hormone treated patients who have no possibility of exploring their treatment wishes with healthcare professionals.

A major strength of this study was that it is the first to investigate hetero-evaluated psychiatric comorbidity together with auto-evaluated mental distress in the same transsexual patients' group. Moreover, this research has examined the relationship between transsexual patients' mental health and cross-sex hormonal treatment in a prospective study for the first time. Prospective studies, in fact, can provide more valid information than cross-sectional studies and more accurately determine the impact of hormonal therapy among transsexual populations.

In few words, the study provides information on psychiatry comorbidity/functional impairment and self-reported anxiety, depression and psychological symptoms of transsexual patients. The study revealed that the majority of transsexual patients have no psychiatric comorbidity. Transsexualism is a diagnostic entity in its own right, not necessarily associated with severe comorbid psychiatric findings. The condition, however, seemed to be associated with subthreshold depression, subthreshold anxiety and substantial functional impairment. Finally, there appeared to be a relationship between cross-sex hormone therapy and better mental health: when treated transsexual patients reported less anxiety, depression, psychological symptoms and functional impairment.

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In this study there is no funding source.

Conflicts of interest

The authors declare that they have no conflicts of interest in the research.

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